Milker’s nodule: an occupational infection and threat to the immunocompromised

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Abstract
Milker’s nodule virus, also called paravaccinia virus, is a DNA virus of the parapoxvirus genus transmitted from infected cows to humans. It results from contact with cattle, cattle by-products or fomites. Classified as an occupational disorder, those at risk of exposure include farmers, butchers and agricultural tourists. The viral infection begins 5–15 days after inoculation as an erythematous-purple, round nodule with a clear depressed centre and a surrounding erythematous ring. While familiar to those in farming communities, the presence of the nodule may be concerning to others, particularly the immunosuppressed. Milker’s nodules are self-limited in immunocompetent individuals and heal without scarring within 8 weeks. Another member of the Parapoxvirus genus, the orf virus, is also transmitted from animals to humans by direct contact. While complications are rare, haematopoietic stem cell transplant recipients are at risk of graft-versus-host disease, as the parapoxvirus may trigger these complications in immunocompromised individuals. In addition, paravaccinia may serve as the antigen source for the development of erythema multiforme. The unique structure and replication process of viruses in the Poxvirus family, while includes the Parapoxvirus genus, have been a focus for treatment of infections and cancer. Manipulation of these viruses has demonstrated promising therapeutic possibilities as vectors for vaccines and oncologic therapy.

Received: 18 June 2017; Accepted: 17 October 2017

Conflits of interest
The authors have no conflict of interest to declare.

Funding Sources
This article has no funding source.

Introduction
The milker’s nodule, also known as pseudowpox, is a disease that results from an infection with paravaccinia. Paravaccinia is a member of the Parapoxvirus genus and Poxivirus family. Those infected share a history of contact with cattle, most notably from touching an infected cow’s udder or nose. Infection has also been reported in those who handle raw beef.1 Transmission of the paravaccinia virus may take place through direct contact with contaminated items, or with live or dead cattle. The virus displays resistance to cold, heat and drying.2,3 The milker’s nodules may also appear in those involved in obstetrical procedures with cattle.4 For this reason, it is considered an occupational viral skin disease. Those infected often report not wearing personal protective equipment when interacting with bovine and ovine.1 Visible lesions on the cattle may be absent, but transmission may still occur.4

While most poxviruses are brick-shaped, the parapoxvirus is ovoid. This virion measures 250-300 nm in length with a prominent nucleocapsid.4,5 The negative-stain electron microscopy of the Parapoxvirus genus reveals a long spicule wrapping around the particles, creating a criss-cross effect described as the M form. The parapoxvirus genome is a linear, double-stranded DNA of 135 kilobase pairs, composed mainly of G and C bases. The immune response to infection does not provide immunity, and the individuals are at risk of recurrence if reinfected.5

Clinical Manifestations
Once infected, the virus has an incubation period ranging from 5 to 15 days. The nodules develop most commonly on areas where skin contact was made with the infected animal, such as the hands and forearms. Most develop between 1 and 5 milker’s nodules after inoculation. Non-immunocompromised patients
are usually asymptomatic, while more commonly systemic symptoms are found in those who are immunosuppressed.\textsuperscript{1}

The cutaneous nodule evolves through six phases, with each phase lasting approximately 6 days (Table 1).\textsuperscript{1,4} Initially, the nodule may go unnoticed or raise little concern (Fig. 1), but as the nodule becomes larger and more striking in appearance (Fig. 2) (Fig. 3), medical attention is often sought. In most cases, after one to 2 months, the nodule will resolve (Fig. 4).

**Histology**

Milker’s nodules are primarily a clinical diagnosis but may be confirmed with histopathology. On histology, the lesions are hyperkeratotic with acanthosis of the epidermis. The upper third of the epidermis has a ballooning pattern and reticulic degeneration, and multilocular vesicles are present. The dermis has mononuclear cells and eosinophils, indicative of an inflammatory infiltrate. Depending on the phase of evolution of the nodule, eosinophils and intracytoplasmic inclusion bodies may not be seen.\textsuperscript{1} Staining of the biopsy specimen with haematoxylin and eosin will show epidermal necrosis with spongiosis, inflammatory cells and intracytoplasmic eosinophilic inclusions.\textsuperscript{4}

**Differential Diagnosis**

A variety of infectious conditions may present similar to milker’s nodules (Table 2). Diagnoses may be distinguished clinically, and treatment differs between conditions. The *Poxviridae* family is a group of double-stranded DNA viruses that include cowpox, vaccinia, variola, monkeypox, molluscum contagiosum, orf and milker’s nodule.\textsuperscript{6} Some of these viruses create cutaneous eruptions that appear similar to milker’s nodules. Most notably is orf, one of the leading differential diagnoses for patients with nodular eruptions following interaction with farm animals.\textsuperscript{7} Orf is commonly transmitted to humans from direct contact with infected sheep and goats. Groups at risk include farmers, veterinarians and butchers. Like the milker’s nodule, it progresses through six stages before spontaneously regressing in 6-8 weeks.\textsuperscript{6} The causative organism is indistinguishable from the organism causing milker’s nodules.\textsuperscript{2} The similarities both clinically and histologically between orf and milker’s nodules have

### Table 1 Classic stages of the milker’s nodule

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage 1: Maculopapular</td>
<td>Single erythematous nodule</td>
</tr>
<tr>
<td>Stage 2: Targetoid</td>
<td>Central papule surrounded by an erythematous outer ring with a pale inner ring</td>
</tr>
<tr>
<td>Stage 3: Acute</td>
<td>Nodule ulcerates and begins to drain</td>
</tr>
<tr>
<td>Stage 4: Regenerative</td>
<td>Nodule becomes firm, black papules develop within the nodule, crusts</td>
</tr>
<tr>
<td>Stage 5: Papillomatous</td>
<td>Papillomas appear in the nodule</td>
</tr>
<tr>
<td>Stage 6: Regression</td>
<td>Nodule begins to regress until it eventually fades away without leaving a scar</td>
</tr>
</tbody>
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There have been four reported cases of human-to-human transmission of the orf virus. Transmission is classically from animal or fomites to humans.\textsuperscript{7,8} While orf resolves spontaneously in approximately 6 weeks, those who are

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*JEADV* 2018, 32, 537-541

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Table 2 Differential diagnoses for milker’s nodule, distinguishing features, and first-line treatments

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing Feature</th>
<th>First-line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orf</td>
<td>Indistinguishable from milker’s nodule. History of contact with infected sheep and goats.</td>
<td>No treatment necessary. May use 4% cidofovir topical cream or imiquimod.8</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Dome-shaped, waxy and umbilicated papules. Most often located on head, neck, trunk and flexor surfaces. Often occurs in children age 2–5 but also adolescents and young adults through skin-to-skin contact and fomites.</td>
<td>Cryotherapy, mechanical curettage, podophyllin/podofilox, cantharidin, iodine and tretinoin.5</td>
</tr>
<tr>
<td>Pyogenic granuloma</td>
<td>Pedunculated, dome-shaped, friable nodule and dark red colour. May resemble melanoma or squamous cell carcinoma so should be biopsied. Can occur with minimal trauma.</td>
<td>Surgical excision, silver nitrate, carbon dioxide or pulsed dye laser.22</td>
</tr>
<tr>
<td>Fish tank granuloma due to</td>
<td>Ulcerating lesion, history of contact with fish or aquariums. Risk is tetracyclin and septic arthritis.</td>
<td>Minocycline, doxycycline, clarithromycin, rifampin and cotrimoxazole.23</td>
</tr>
<tr>
<td>Mycobacterium marinum</td>
<td>Most commonly reported in Australia and Africa in children less than 15 years of age. Initially described as firm and painless nodules, papules or plaques but can progress to an ulcer with a necrotic base over a 1–2 month period.</td>
<td>Rifampin + streptomyacin, wide excision (+/- rifampin), rifampicin + moxifloxacin or clarithromycin or ciprofloxacin, ciprofloxacin + clarithromycin.25</td>
</tr>
<tr>
<td>Buruli ulcers due to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium ulcerans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly Growing</td>
<td>May occur after surgery, percutaneous catheter insertion or inoculation. Dark red nodules that progress to abscesses that drain clear fluid. Culture of the lesion will show mycobacteria visible to the naked eye within 7 days of culture.</td>
<td>M. fortuitus: clarithromycin + levofloxacin or amikacin ciprofloxacin levofloxacin trimethoprim</td>
</tr>
<tr>
<td>Mycobacterium –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mycobacterium fortuitous,</td>
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<tr>
<td>mycobacterium chelonae and</td>
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<tr>
<td>mycobacterium abscessus.</td>
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<tr>
<td>Anthrax by Bacillus anthracis</td>
<td>Transmitted by subcutaneous contact with spores from infected animal hides and soil. After a 7 days incubation period, a rapidly growing necrotic ulcer with black eschar will form. Additional symptoms are of local oedema, regional lymphadenopathy and lymphangitis.</td>
<td>Amoxicillin, levofloxacin and ciprofloxacin.24</td>
</tr>
<tr>
<td>Tularemia caused by</td>
<td>Transmitted through contact with rabbits or rodents via an arthropod vector. A rapidly growing painful red papule with central necrosis develops. Fever and lymphadenopathy are often present.</td>
<td>Ciprofloxacin, doxycycline, streptomycin or gentamicin.25</td>
</tr>
<tr>
<td>Francisella tularensis</td>
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</tr>
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</table>

immunocompromised may progress through a longer course and require medical intervention such as topical imiquimod or curettage and shave excision.4,10 It has been hypothesized that those with a history of atopic dermatitis have a higher risk of contracting orf as their barrier and immune function is impaired.8

Other members of the Parapoxirus genus may be transmitted to humans by contact with animals. While orf and milker’s nodules are the most common worldwide, non-farm animals may also carry parapoxviruses. For example, parapox of camels can produce Ausdyk disease, seals may transmit sealpox, and deer of New Zealand and the United States have been found to carry an associated parapoxvirus that has been transmitted to hunters. Similar to the pseudopoxvirus causing milker’s nodules, bovine also carries the poxvirus subtype, vaccinia. Co-infection with both vaccina and pseudopoxvirus within a single lesion may occur.11

Parapoxviruses in immunocompromised patients

While milker’s nodules are relatively benign in healthy individuals, expression in immunocompromised hosts varies. Following a haematopoietic stem cell transplant, patients who contract the parapoxvirus that causes milker’s nodules may develop erythema multiforme and graft-versus-host disease. One such patient developed painless nodules on the dorsum of the hand and painful ulcers in the mouth. He reported contact with the mouth of a calf which had visible ulcerating lesions. The symptoms of erythema multiforme and graft-versus-host disease improved only after aggressive immunosuppression with prednisone and tacrolimus. Viral infections and viral reactivations have been implicated as the triggers to graft-versus-host disease after a haematopoietic stem cell transplant.12–15 Among immunosuppressed patients, the milker’s nodule virus may also trigger an erythema multiforme reaction.16

Parapoxvirus in disease therapy

The Poxvirus family has been studied for use in therapies against other viral and bacterial infections. The parapoxvirus, orf, is in preclinical trials for use as a vector for vaccines against various viral and bacterial pathogens, including influenza A, rabies, the
pseudorabies virus, Borna disease, rabbit viral haemorrhagic disease, and classic swine fever virus.17

Poxviruses are also being studied for use in cancer therapy. Poxviruses are large enveloped viruses, allowing easy manipulation of the virus' genes, such as deleting specific viral genes and genetically installing tumour selective oncolytic properties. Recently, the vaccinia virus, a member of the Poxvirus family, demonstrated the ability to replicate in and destroy cancer cells.18

The orf virus has properties that make the virus an ideal choice for cancer therapy. The virus stimulates the innate and adaptive antitumour immune response, yet even after forming antibodies to the virus, can cause repeated infections. Further, the isolated regenerative wound with extensive vasculature found in the orf nodule is similar to that of a tumour.19

**Treatment**

As the majority of cases of milker's nodules resolve spontaneously, watchful waiting should be initially employed to avoid overtreatment. Idoxuridine and imiquimod topical creams stimulate the immune system and provide a local antiviral response and may serve as a treatment option before considering cryosurgical ablation or surgical excision. For those with either a large lesion or a weak immune system, alpha-interferon injections into the lesion or cidofovir cream may be beneficial. Patients should be provided with education about the importance of hand hygiene and use of protective equipment.20

**Conclusion**

It is pivotal to make the correct diagnosis of milker's nodule when deciding on appropriate treatment. Similar appearing conditions are treated using antibiotics or surgeries, and an incorrect diagnosis can lead to unnecessary treatment and disfigurement if surgery is performed. Those working with animals in the farming industry are familiar with the skin manifestations of orf and milker's nodules, while others in contact with infected animals may be perplexed by the nodular eruption.2 While in most, inoculation with the parapoxvirus is self-limiting, those who are immunocompromised may develop graft-versus-host disease or erythema multiforme. Atypical or particularly aggressive manifestations of viral infections may occur in patients with immunodeficiency (e.g. after transplantation) as well as patients whose immune response has been altered (e.g. pregnant women).21 With an increased number of individuals undergoing a haematopoietic stem cell transplant, precipitation of graft-versus-host disease, as it relates to a viral trigger, mandates physicians be aware of atypical cases such as orf and milker's nodules as possible inducers of graft-versus-host disease.12 The Parovirus family and Parapoxvirus genus of which paravaccinia virus belongs have been gaining attention in its role as a vaccine vector and role as a potential cure for cancer.

**References**

